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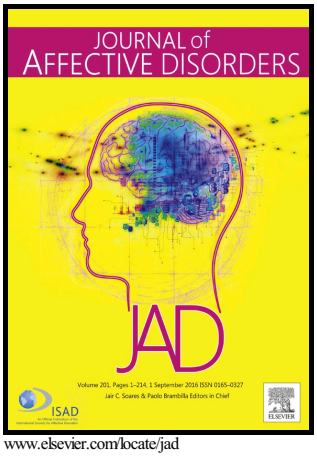

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Resting-State Meta-Analysis in Borderline Personality Disorder: is the fronto-limbic hypothesis still valid?

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To the editor,

Visintin et al. (Visintin et al. 2016) recently published a stimulating meta-analysis of the studies investigating the abnormalities in brain activity at rest in patients with borderline personality disorder (BPD). This study is important to shed some light on the neurobiology of BPD, which has been little investigated despite its high prevalence (0.5–5.9% of the general population) and severity (Amad et al. 2014).

To disentangle the contradictory findings reported in the 7 resting-state studies included in their meta-analysis (4 fMRI studies and 3 PET studies), Visintin et al. converted the reported peak coordinates to effect-size maps and then voxelwise meta-analyzed the maps using Seed-based d Mapping (SDM) (Radua et al. 2012; Radua et al. 2014).

The authors found an increased activity in patients with BPD relative to healthy controls (HC) in anterior cingulate cortex, medial prefrontal cortex, and precuneus/posterior cingulate gyrus and a decreased activity in right lateral temporal cortex, inferior temporal gyrus, orbitofrontal cortex and dorsolateral prefrontal cortex.

After reading the meta-analysis, however, we wondered whether results would be roughly similar if other selections of studies had been applied. Specifically, we wonder whether results would be similar if: **a)** the authors had included a PET study by Juengling et al. (Juengling et al. 2003), which

studied brain metabolism at baseline in 12 medication-free BPD, without current substance abuse or depression, compared to 12 HC and **b)** had excluded the study by Soloff et al. (Soloff et al. 2005), given that its inclusion as a resting-state study might be thought by some readers to be limited by the fact that this was an experimentation of fenfluramine vs placebo and some evidence shows that placebo can alter the resting state (e.g.(Sikora et al. 2016; Schmidt-Wilcke et al. 2014)).

Thus, we replicated the meta-analysis using the same methodology than Visintin et al., but including the study of Juengling et al. and replacing the study of Soloff et al. (Soloff et al. 2005) by a FDG-PET study in 13 BPD and 9 healthy controls published by the same group in 2003 (Soloff et al. 2003).

To identify the studies eligible for this re-meta-analysis, a systematic search was conducted on the Medline and ISI Web of Knowledge up to September 2016 using the following search term combinations: (1) ‘‘neuroimaging’’, ‘‘fMRI’’, ‘‘PET,’’ (2) ‘‘resting-state’’, ‘‘default network’’ and (3) the terms ‘‘borderline personality disorder’’. We included peak coordinates and effect sizes resulting from whole-brain analyses, whereas studies using seed-based analysis procedures were excluded. Eight studies were included (see full description in **Supplementary Material**). The functional neuroimaging meta-analysis was performed by using SDM software (www.**sdm**project.com) with the same parameters than Visintin et al. (500 permutations, $p < 0.005$, $|SDM\text{-}Z| > 1$, spatial extent > 20 voxels). To assess heterogeneity between studies, I^2 values were extracted from the meta-analytic peaks. *Jackknife sensitivity analyses, consisting of iteratively repeating the meta-analysis excluding one study at a time, were also conducted to examine the robustness of the main meta-analytic output.*

In agreement with the earlier meta-analysis by Visintin et al., we also found an increased activity in patients with BPD relative to HC in the anterior cingulate cortex (MNI coordinates x = 6, y = 44, z = 12). We also found an increased activity in left inferior (-54, 8, 10) and superior (-8, 54, 24) frontal gyri, and conversely to the results of Visintin et al., a reduced activity in the posterior cingulate gyrus (0, -26, 28) and in the right precuneus (6, -72, 42) (see Figure). Heterogeneity

between studies was moderate in the anterior cingulate cortex (I2 = 48 %) and the left inferior gyrus (I2 = 38 %) and was not seen in the posterior cingulate gyrus and in the right precuneus. *Jackknife sensitivity analyses showed that the main findings were highly replicable across combinations of datasets. Indeed, the increased activity in BPD patients in anterior cingulate cortex, left inferior and superior frontal gyri were preserved throughout all combinations of the data sets. Results in the right precuneus and the posterior cingulate were significant in all but one combination.*

These results contrast with the classic fronto-limbic hypothesis of BPD which postulates a decreased activity of frontal brain regions and a limbic hyperactivity. The brain regions found here may correspond to networks involved in pain processing (Kluetsch et al., 2012) and dissociative states (i.e. disintegration of perception, consciousness, identity and memory) which resembles the findings in participants with post-traumatic stress disorder (PTSD) while in dissociative states (Ludäscher et al., 2010). Interestingly, dissociation, which provides subjective detachment from overwhelming emotional experience during and in the aftermath of trauma, also occurs in up to two thirds of BPD patients (Vermetten and Spiegel, 2014). *Furthermore, the prevalence of childhood trauma is so frequently associated with BPD (either neglect (92%), sexual abuse (40%-70%) or physical abuse (25%-73%) that it has often been described as being conceptually and phenomenologically similar to PTSD* (Amad et al., 2016)*. In particular, these two disorders present numerous striking similarities at the etiological, clinical and neurobiological levels. On a neuro-functional level, Wang et al. recently published a meta-analysis of functional imaging in PTSD and found an increased resting-state brain activity in frontal regions in PTSD patients in comparison with trauma-exposed subjects without PTSD (Wang et al. 2016). Some of these frontal regions seem to be the same as found in our meta-analysis.* Taken together, these findings could then reinforce the hypothesis that BPD is conceptually and phenomenologically similar to PTSD and that BPD and PTSD might be two sides of the same coin where the main key difference between these disorders is the age at which traumas occur, which can differentially affect the brain connectivity and thus the psychiatric symptoms (Amad et al., 2016). Nevertheless, these results require cautious interpretation

and should not be considered as definitive in BPD. Indeed, BPD has a potentially high clinical heterogeneity. For example, with nine DSM-5 criteria and a threshold for five positive criteria of a diagnosis of BPD, there are 151 theoretical possible ways of diagnosing this disorder. BPD has also been associated with child abuse and many comorbidities, including mood disorders, anxiety disorders, and PTSD, and the results therefore can hardly be attributed solely to the BPD. Moreover, BPD comorbidities differ between men and women. For example, men more often display substance use disorders, and women more frequently present affective, anxiety, and eating disorders (Amad et al. 2014). Future studies should focus on the clinical assessment of carefully selected BPD patients to explore specific dimensions and refined phenotypes (e.g., social cognitive impairment, hallucinations, impulsivity, suicidality or severity of the disorder) to improve the comprehension of the neurobiology of BPD.

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FIGURE CAPTION: Regions of increased (red) and decreased (blue) activation at rest in patients with borderline personality disorder compared with healthy controls. Statistical maps are thresholded at $p < 0.005$ and $k > 20$.